REMARKS

Status of the claims

Claims 1-2, 4-5, 10, 12-14 and 16 are pending. Claims 1-2, 4-5, 10, 12-14 and 16 are rejected. Claims 1, 5, and 10 are amended. Claims 2-3, 6-9, 11, and 13-21 are canceled. No new matter is added.

Claim amendments

Claim 1 is amended to overcome rejections under 35 U.S.C. §102(b) & §103(a) such that the combinations of the R^1-R^5 moieties comprising the structure do not encompass those structures disclosed in **Davidsen** et al., either directly or as homologs, as discussed infra. Claim 10 is amended to overcome rejections under 35 U.S.C. §112, first and second paragraphs, as discussed infra. Claims 13-14 and 16 are canceled.

Claim 5 depends from claim 1 and is amended to correct spelling in step i). The specification and figures, as discussed infra, teach that N-hydroxysuccinimide is used and not hydroxysuccinamide. Claim 5 is also amended for clarity in step j) to refer to "optionally *O*-protected" as recited in step i). Claim 10 is amended to overcome rejection under 35 U.S.C. §103(a) & §112, first paragraph such that the claim is drawn to a method of inhibiting growth of tumors using the compounds of amended claim 1, as discussed infra.

Claim objections

Claims 1-2, 4-5 are objected to as containing non-elected subject matter in the starting material 2,5-dioxo-pyrrolidinyl ester of step (a) of claim 5. Applicants respectfully draw the Examiner's attention to the entirety of step (a) in claim 5 which is drawn to the formation of an optionally *O*-protected R^1-1-carbonyl-C2-(R^2)-methyleneamine from R^1 and an *N*-protected R^2-amino acid 2,5-dioxo-pyrrolidinyl ester. As shown in Figures 3A-3B, the 2,5-dioxo-pyrrolidinyl moiety is not a non-elected R^1 pyrrolidinyl moiety, but rather is derived from *N*-hydroxysuccinimide (**7**) and is used to protect carboxyl oxygens in Fragments A and B and in the coupled Fragment A + B. It functions as a leaving group in the presence of an R^1 nitrogen or other nitrogen to form the optionally *O*-protected R^1-1-carbonyl-C2-(R^2)-methyleneamine in step (a) or as a leaving group when joining Fragments A and B in step (g). Neither *N*-hydroxysuccinimide nor the resulting 2,5-dioxopyrrolidinyl moiety becomes part of the final product. Thus, it is not a non-elected starting material and its inclusion in the claimed method is proper. Additionally, Applicants respectfully submit that the method in claim 5 is a method of synthesis of the compounds in amended claim 1 and that, provided that the method steps and the products are novel and non-obvious, the starting materials are irrelevant.

The 35 U.S.C. §112 rejections

Claims 10 and 14 are rejected under 35 U.S.C. §112, as failing to comply with the written description requirement. Claims 10 and 14 are rejected

under 35 U.S.C. §112, as containing subject matter which was not described in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner states that the claims 10 and 14 contain subject matter, i.e., "neoplastic disease" or "tumor cell" without disclosing processes of using by naming a cancer or type of tumor cell. The Examiner also states that without disclosing a named cancer or tumor cell the level of ordinary skill is high with little predictability in the art or little direction and guidance for one of skill in the art because no enablement nor support is found in the specification for many diseases. The Examiner suggests that amending claims 10 and 14 to recite ovarian carcinoma would obviate the rejections.

Applicants have canceled claims 13-14 and amended claim 10 to recite a method of inhibiting the growth of a tumor in an individual and to recite specific cancers. The specification demonstrates the growth inhibitory properties both *in vitro* and *in vivo* for both solid and disseminated cancers such as ovarian, prostate, mammary, head and neck squamous cell carcinoma, non-small-cell-lung-cancer squamous cell carcinoma, non-small-cell-lung-cancer adenocarcinoma, lymphoma and acute myeloid leukemia (pg. 65, ll. 12 to pg. 69, ll. 14). It is well within the skill of one of ordinary skill in the art to treat any mammary cancer, head and neck cancer, squamous cell carcinoma, adenocarcinoma, lymphoma and leukemia, generally, given these teachings. It also is well within ordinary skill and is standard in the art to determine dose and a dosage regimen for administration of a therapeutic anticancer compound.

Accordingly, in view of the amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 10 and 14 under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §102(b) rejection

Claims 1-2, 4-5, 10, 12-14, and 16 are rejected under 35 U.S.C. §102(b) as being anticipated by **Davidsen** et al. (U.S. Patent No. 5,985,911). Applicants respectfully traverse this rejection.

The Examiner states that **Davidsen** et al. clearly anticipate compounds of the instant claim 1 where R^1 is optionally substituted indole or pyrrole, R^2 is benzyl or C(CH3), R^3 is C_{3-8} alkyl or C_{3-8} alkyl optionally substituted with straight or branched or cyclic hydrocarbon chains, R4 is C_{1-3}alkyl optionally substituted with straight or branched or cyclic hydrocarbon chains (pg. 7, ll. 18-19 in Applicants' specification for R^3 and R^4) and R^5 is OH or NHOH.

Applicants have canceled claims 2, 13-14 and 16. Applicants' amended claim 1 and claim 4 recite a compound or a pharmaceutical composition thereof having a structure where R^1 is only indoline or an optionally substituted or halogenated indole, pyrrole, or imidazole, R^2 is amended to delete alkyl, phenyl, benzyl, and naphthyl moieties, R^3 is unchanged, R^4 is amended to recite methylene, ethylene and propylene as the specific alkylene moieties, and R^5 is amended to delete -OH and –NHOH moieties.

Amended claim 5 recites a method of asymmetric synthesis using Evan's chiral auxiliary and N-hydroxysuccinimide to synthesize, and

subsequently couple, fragments of the compounds to form the compounds. *N*-hydroxysuccinimide is used to form a 2,5-dioxo-pyrrolidinyl ester with unprotected carboxyl oxygens, i.e., the hydroxy oxygens, which bond with R^1 or other nitrogens later in the synthesis thereby reforming the N-hydroxysuccinimide. Fragment A is a pseudodipeptide, Fragment B is a dicarboxylic acid derivative and Fragment C is a suitably protected amine or derivative thereof (pg. 22, ll. 7-13; Fig. 1B and 3A-3C).

Fragment A, an R^1-1-carbonyl-C2-(R^2)-methyleneamine, is synthesized by adding R^1 to an *N*-protected R^2-amino acid 2,5-dioxo-pyrrolidinyl ester and deprotecting the *N*-protected R^2-amino acid. Evan's chiral auxiliary **2** and N-hydroxysuccinimide **7** are used to synthesize Fragment B, generally a C2(R^3)-R^4-dicarboxylic acid *tert*-butyl ester-(2,5-dioxo-pyrrolidin-1-yl) ester (pg. 22, ll. 19 to pg. 23, ll. 4). Fragments A and B are coupled to form R^1-1-carbonyl-C2(R^2)-carbamoyl-methylene(R^3)-R^4-carboxylic acid 2,5-dioxo-pyrrolidin-1-yl ester. The addition of Fragment C produces R^1-1-carbonyl-C2(R^2)-carbamoyl-methylene(R^3)-R^4-carbonyl-R^5 and N-hydroxysuccinimide.

The overall synthetic method in **Davidsen** et al., as shown in Scheme 1 (col. 16), couples a tert-butyl ester of a succinic acid derivative **1**, synthesized as in Scheme 3 (col. 17), with the ketoamine **2**, synthesized as in Scheme 2 (col. 17), and subsequently adds the hydroxy or hydroxylamine functionality. **Davidsen** et al. do not form 2,5-dioxo-pyrrolidinyl esters with unprotected carboxyl oxygens during the synthesis of either **1** or **2** nor during coupling of **1** or **2**.

At a minimum, absent teachings of Applicants' amended R^5 moieties **Davidsen** et al. cannot anticipate amended claim 1 and claim 4. As amended claims 10 and 12 depend directly and indirectly, respectively, from amended claim 1 and as the compounds disclosed in **Davidsen** et al. do not anticipate Applicants' compounds, then **Davidsen** et al. cannot anticipate the use of these compounds to inhibit growth of tumor cells in an individual. In considering amended claim 5, the synthetic method in **Davidsen** et al. does not teach Applicants' method. Absent a teaching of using N-hydroxysuccinimide in the synthetic schema, **Davidsen** et al. cannot anticipate amended claim 5.

Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 1, 4-5, 10, and 12 under 35 U.S.C. §102(b) as being anticipated by **Davidsen** et al. be withdrawn.

The 35 U.S.C. 103(a) rejections

Claims 1-2, 4-5, 10, 12-14 and 16 are rejected under 35 U.S.C. 103(a) as being obvious over **Davidsen** et al. Applicants respectfully traverse this rejection.

The Examiner states that **Davidsen** et al. disclose C-terminal ketones as inhibitors of MMPs as treating cancer. The Examiner states the substituents on the ketone backbone of the compounds in Davidsen et al. are where W is –NHOH or –OH, V is oxygen, R1 and R2 are independently hydrogen or alkyl, R3 is alkyl, unsubstituted or substituted phenyl or phenylalkyl, R4 is

hydrogen or alkyl, R5 is alkyl, phenyl or substituted phenyl, R6 is indolyl, substituted indolyl, pyrrolyl, imidazolyl, or substituted imidazolyl (col. 120-132). The Examiner states that **Davidsen** et al. teach that the matrix metalloproteinase inhibitors disclosed therein treat cancer, including tumor growth, metastasis or invasion (col. 1, ll. 40-50).

Davidsen et al. state that matrix metalloproteinases are a class of extracellular enzymes including collagenase, stomelysin and gelatinase and are believed to be involved in tissue destruction in, *inter alia*, cancer (col. 1, ll. 20-24). **Davidsen** et al. further state that typical connective tissue cells are embedded within an extracellular matrix of high molecular weight proteins and glycoproteins and where the matrix is maintained by a series of processes including cell division, matrix synthesis and matrix degradation. In the case of cancer, a lack of co-ordination of these events can allow tumor cells to become invasive and penetrate the basement membranes of surrounding capillaries leading to subsequent metastasis (col. 1, ll. 26-39).

Davidsen et al. do not teach Applicants' compounds as recited in amended claim 1. These compounds are sufficiently different that one of ordinary skill in the art could not be motivated to synthesize them as obvious homologs. One of ordinary skill would have to find a teaching or suggestion to replace at least both R^2 and R^5 with substituents that are not obvious homologs or variants of corresponding positions in the compounds of **Davidsen** et al. No such teaching or suggestion is found.

Applicants' R^2 moiety corresponds to R^5 in **Davidsen** et al. R^5 encompasses hundreds of substituents which generally are alkyl, substituted alkyl, phenyl and substituted phenyl (col. 5, ll. 50 to col. 6, ll. 17). **Davidsen** et al. neither teach nor suggest that R^5 may be a nitrogen heterocycle or substituted nitrogen heterocycle as in Applicants' amended claim 2. Also, Applicants R^5 moiety corresponds to W in **Davidsen** et al. W is specifically taught as hydroxy or hydroxyamine. As amended, Applicants' R^5 is a substituted amide. Thus, one of ordinary skill in the art only could synthesize Applicants' compounds, as recited in amended claim 1, by trying different combinations of substituents which has long been held not to be the standard under 35 U.S.C. 103(a).

Applicants have canceled claim 2. Claim 4 depends from amended claim 1 and limits the compounds in amended 1 as comprising a pharmaceutical composition. If amended claim 1 is novel and non-obvious over **Davidsen** et al., then so is dependent claim 4.

Claim 5 depends from amended claim 1 and limits the synthetic method recited therein to synthesis of the compounds in amended claim 1. At a minimum, because Applicants maintain that amended claim 1 is both novel and non-obvious over **Davidsen** et al., dependent claim 5 is likewise non-obvious. Nonetheless, absent motivation to synthesize amended claim 1 compounds, as discussed supra, Applicants state that one of ordinary skill in the art would find no motivation to alter the synthetic method.

Davidsen et al. teach that the matrix metalloproteases are synthesized by known methods. In the synthetic schema presented in **Davidson**

et al. the carbonyl oxygen in the succinate ester 1 corresponding to Applicants' structures specifically are left unprotected when coupled with the keto-amine 2 in Scheme 1 (col. 16, ll. 21-59). Nor are corresponding carbonyl oxygens protected during the synthesis of the succinate ester and the keto-amine (col. 17, ll. 1+). Without a suggestion or teaching to alter the synthesis to protect these oxygens, a skilled artisan again merely would be trying in altering the synthetic schema.

Applicants have canceled claims 13-14 and 16. Applicants have amended claim 10, as discussed supra. Claims 10 and 12 depend directly and indirectly from amended claim 1 and limits the method of inhibiting tumor growth to the use of those compounds in amended claim 1 and limits the individual to a human or an animal. Applicants submit that amended claim 1 is novel and inventive over **Davidsen** et al. and thus dependent claims 10 and 12 also are non-obvious.

Nonetheless, Applicants submit that the enzymes inhibited by the matrix metalloproteinases taught in **Davidsen** et al. were well-known in the art prior to the time of the instant invention to be expressed by tumor cells which have broken away from the primary tumor and which attach to the extracellular matrix, which separates the tumor from adjoining tissue. These tumor cells degrade or destroy proteins comprising the extracellular matrix via these enzymes. These enzymes breach the extracellular matrix to facilitate motility, invasiveness and metastasis of tumor cells from well-advanced tumors.

Inhibitors of these enzymes would prevent breach or degradation of the extracellular matrix and subsequent invasion and/or metastasis of tumor cells and thereby prevent growth of new or metastatic tumors. However, the matrix metalloproteases in **Davidson** et al. would not inhibit the growth of the primary tumor. Thus, even should one of ordinary skill in the art find motivation in **Davidsen** et al. to synthesize Applicants' compounds, Applicants submit that such a skilled artisan would not find a demonstration that the matrix metalloproteases in **Davidsen** et al. inhibit stromelysin as reasonably predictive that these compounds would inhibit the growth of established tumors, particularly in view of what is known in the art.

Absent a teaching or suggestion to motivate one of ordinary skill in the art to synthesize Applicants' compounds using Applicants' method, as encompassed by amended claim 1, without merely trying and absent a reasonable expectation of success of inhibiting growth of an established tumor with matrix metalloproteinases in view of what is known in the art, prima facie obviousness over **Davidsen** et al. has not been established. Accordingly, in view of the amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 1, 4-5, 10, and 12 under 35 U.S.C. 103(a) as being obvious over **Davidsen** et al. be withdrawn.

This is intended to be a complete response to the Office Action mailed July 22, 2004. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution. Applicants believe no fees are due, however, please

debit any applicable fees from Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

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